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Review article

SYNTHESIS OF N-BENZAMIDOMETHYL - 4 -TOLUENESULFONAMIDE BY TWO DIFFERENT SYNTHETIC METHODS

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Abstract

Sulfonamide drugs paved the way for the antibiotic revolution in medicine. The sulfonamide chemical part is also present in other medications that are not antimicrobials, including thiazide diuretics, loop diuretics, anti-diabetic drugs, COX-2 inhibitors, etc.
To make new derivatives of sulfa-drugs, test reactions by different synthetic procedures were performed to obtain *N*-benzamidomethyl-4-toluenesulfonamide. By two different synthetic procedures, *N*-benzamidomethyl-4-toluenesulfonamide was obtained in high yields. Reaction) with 4-toluene sulfonamides and (benzamidomethyl)triethylammonium chloride were performed at room temperature in ethanol/water solutions (pH ≥ 9). The other synthetic method was performed in dichloromethane or water depending on the solubility of *N*-benzamidomethylamine.
The structure of *N*-Benzamidomethyl -4-toluenesulfonamide was confirmed and characterized by IR, 1H–NMR, 13C–NMR, UV, and MS spectrometry.

Keywords: sulfonamide, benzamidomethyl, derivative

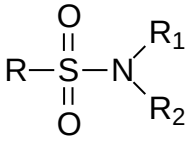
1. Introduction

In the pharmaceutical industry, new organic molecules are synthesized in the hope that some of them may be useful new drugs. In the chemical industry, syntheses are performed to find more economical ways to obtain known compounds. Complex molecules are synthesized in academic laboratories, sometimes out of a purely intellectual challenge and the mastery of new techniques.

The foundation of the therapy with chemical means began in the beginning of the 20th century by Paul Ehrlich [1], especially with his discovery in 1907 of the healing properties of some dyes which were sulfonamides.

In 1935, Gerhard Domagk [2] synthesized the sulfonamide called Prontosil, which inhibits the growth of streptococci.

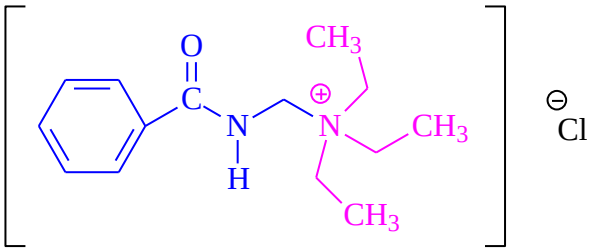
Sulfonamides are compounds that are represented by a general formula:



This research work aimed to investigate possible and most efficient synthetic routes for obtaining benzamidomethyl derivatives of toluene sulfonamide as an introduction to further research for obtaining new N-benzamidomethyl sulfonamide derivatives with potential biological activity.

One of the synthetic routes includes benzamidomethylation reactions of toluene sulfonamide with (benzamidomethyl)triethylammonium chloride, as well as some N-substituted derivatives of toluene sulfonamide.

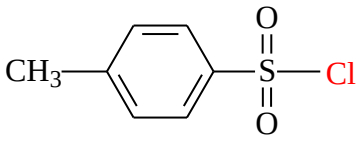
This salt (Structure 1) is highly reactive in aqueous environment under relatively mild reaction conditions. The benzamidomethyl group, which directly replaces the hydrogen atom of the nucleophilic group at the substrate, is marked with a blue color, and the triethylamino group, which "leaves" with a purple color.



Structure 1. (Benzamidomethyl)triethylammonium chloride

The benzamidomethyl group is also found in many compounds with physiological activity that show antivirus [3,4], antitumor [5], antifertility [6], antibacterial properties [7,8], acting on bacteria of the Staphylococcus aures family, antibiotic [9,10], non-European [11] and other actions [12,13].

The other synthetic route includes reactions of toluenesulfonyl chloride with benzamidomethyl amines, i.e. some N-substituted derivatives of benzamidomethyl amine. Toluenesulfonyl chloride is an organic compound represented by the following formula where the leaving atom is marked in red.



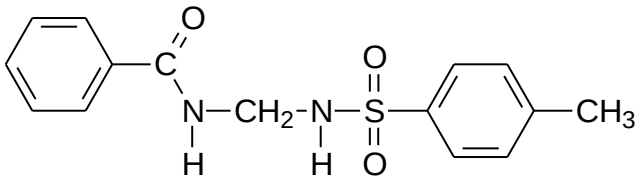
Structure 2. Toluenesulfonyl chloride

2. Experimental procedure

At the very beginning, during the preparation of this scientific paper, the synthesis of (benzamidomethyl) triethylammonium chloride was approached.

This compound was used not only as a reagent for the benzamidomethylation of toluenesulfonamides but also to obtain the corresponding benzamidomethylamines which were further used as nucleophiles in reactions with toluenesulfonyl chloride.

Syntesis of –N-benzamidomethyl-4-toluensulfonamide



Method A: To a concentrated aqueous solution of (benzamidomethyl)amine (~2.40 g; 16.0 mmol) synthesized previously was added well-dusted toluenesulfonyl chloride (1.430 g; 7.50 mmol).

The suspension was vigorously stirred for 5h. The resulting crystals were collected by filtration under reduced pressure. The yield of the air-dried crude product was 85.0% with a melting point of 162.5–164 °C. Purification was performed with ethanol. Pure N -benzamidomethyl-4-toluenesulfonamide had a melting point of 163–164 °C. The yield after recrystallization was ~83.2%.

Method B: To a solution of 1.444 g (8.4 mmol) of toluenesulfonamide dissolved in 30 mL of water was added a solution of 1.523 g (5.62 mmol) of (benzamidomethyl)triethyl-ammonium chloride dissolved in 10 mL of water. A few drops of TEA (pH ≥ 9) were added to this mixture. The mixture was stirred intensively for 4 hours at room temperature. Over time, colorless crystals of the product were observed. The pH of the solution was also monitored at the same time. If the solution became more acidic, a few drops of TEA were added to make the pH ≥ 9. After the fourth hour, water was added to precipitate all the product, however, the excess toluenesulfonamide was partially precipitated as well. The yield of the air-dried crude product was 91.3% with a melting point of 162.5–164 °C. Since toluenesulfonamide dissolves well in ethanol and the product is less so, purification was performed by recrystallization of the crystals from ethanol. Pure *N*-benzamidomethyl-4-toluenesulfonamide was in the form of colorless small crystals with a melting point of 163–164 °C. The yield after recrystallization was ~90.1%.

The new compound *N*-Benzamidomethyl -4-toluenesulfonamide was confirmed and characterized by IR, 1H –NMR, 13C –NMR, UV, and MS spectrometry.

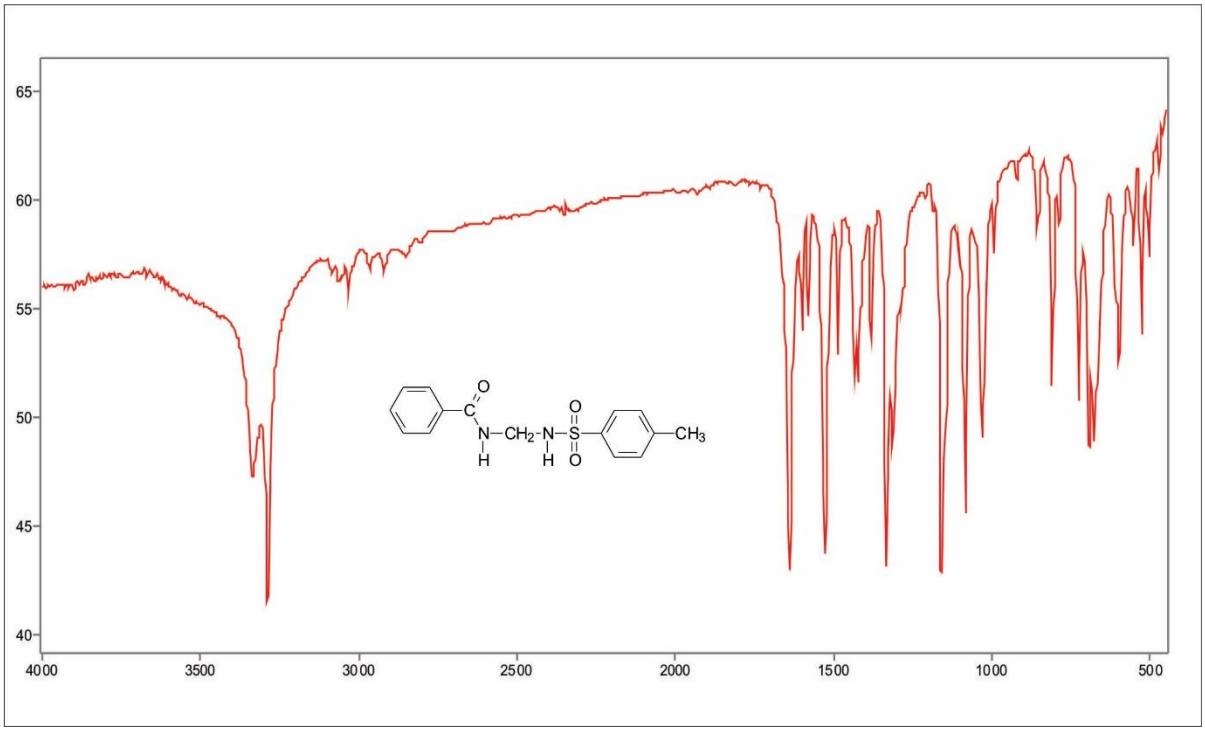


Figure 1. Infrared spectrum of *N*-benzamidomethyl-4-toluenesulfonamide

Infrared spectrum (Figure 1):

(KBr / cm-1); 3337 ν(N–H); 3290 ν(N–H); 1640 Amide I; 1530 Amide II ; 1162 ν(S=O)

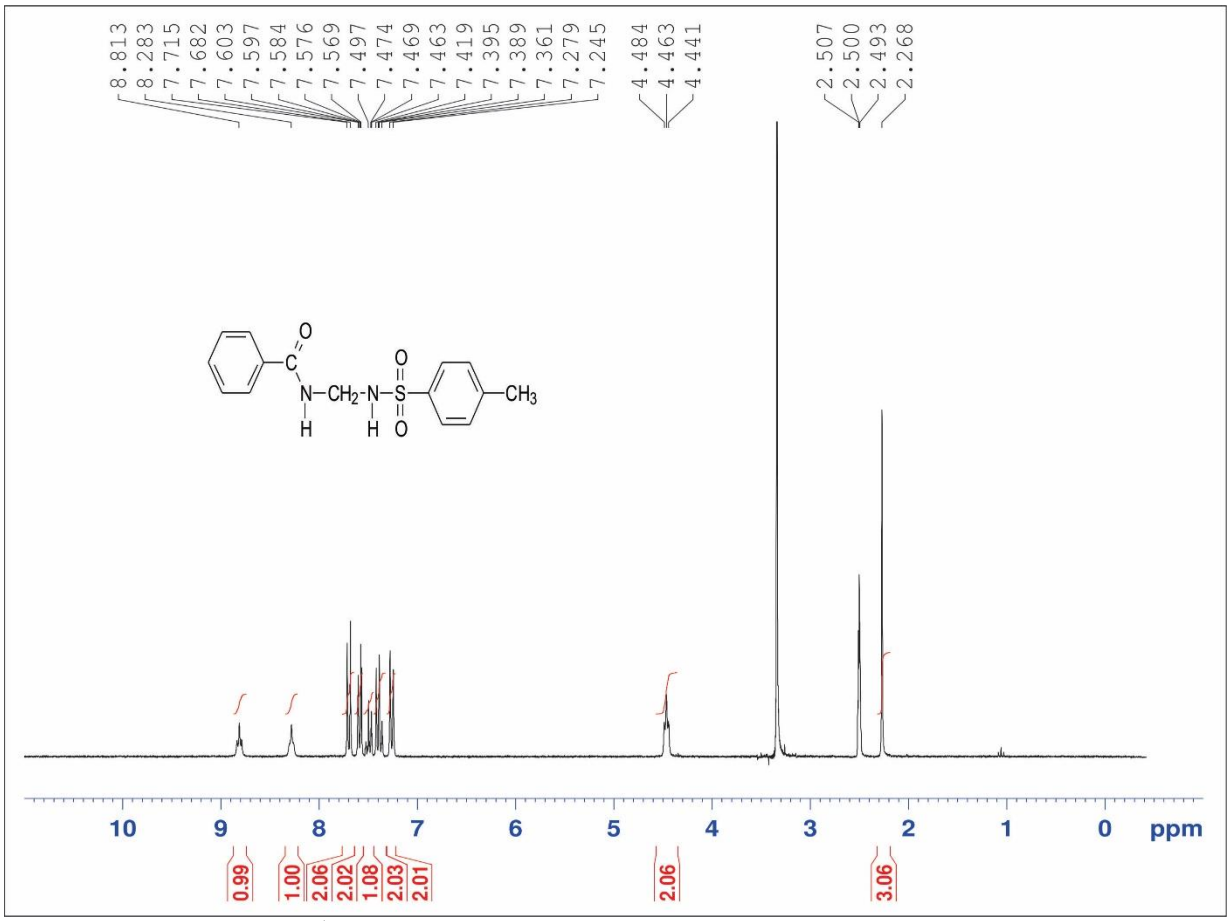


Figure 2. ^{1}H–NMR spectrum of N-benzamidomethyl-4-toluenesulfonamide

^{1}H–NMR spectrum (Figure 2): (DMSO–d_6 / ppm); 8,81 (1H, t, NH); 8,28 (1H, t, NH); 7,71–7,24 (9H, Ar); 4,46 (2H, t, CH_2); 2,27 (3H, s, CH_3);

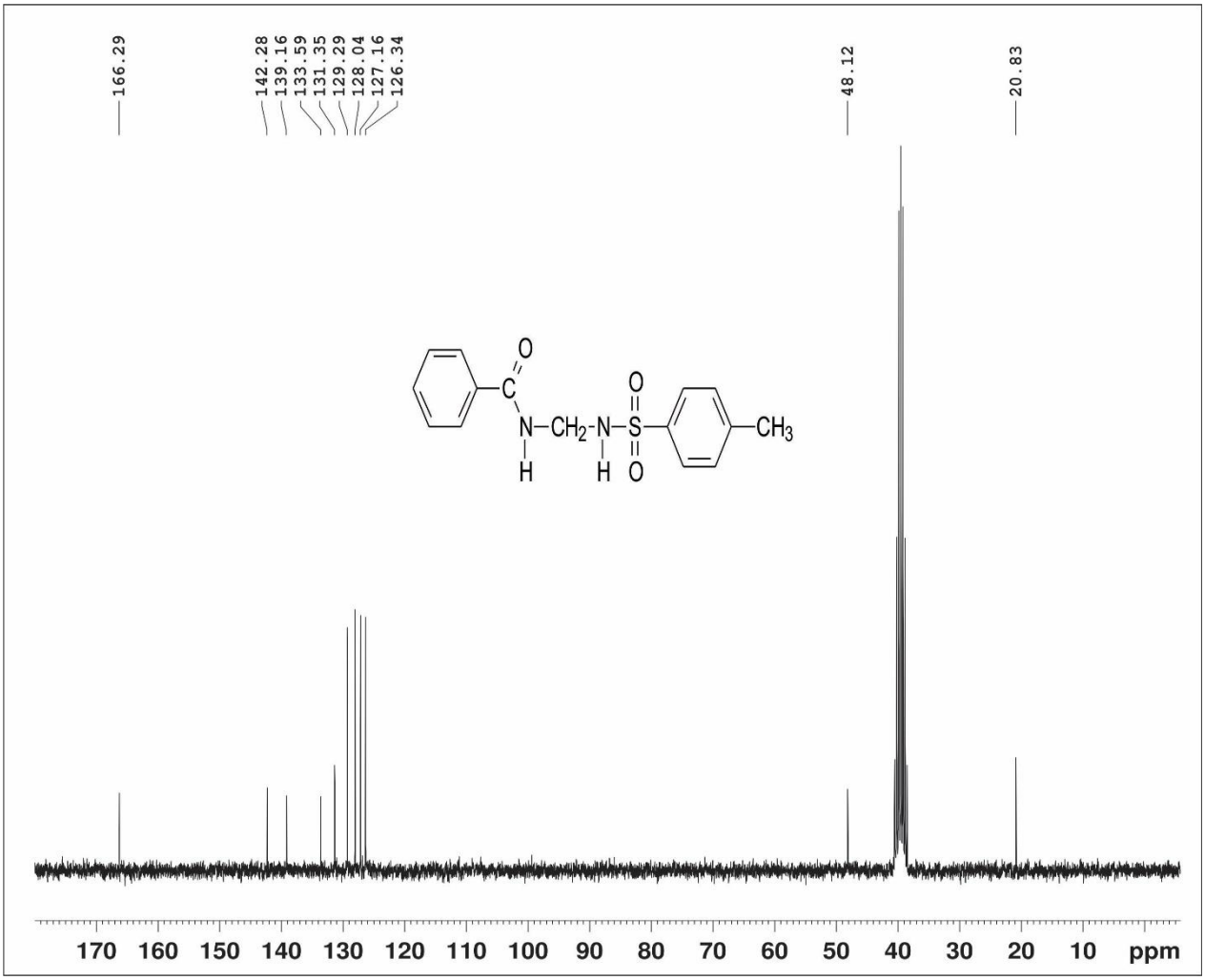


Figure 3. ^{13}CNMR spectrum of N-benzamidomethyl-4-toluenesulfonamide

^{13}C–NMR spectrum (Figure 3): (DMSO–d_6 / ppm); 166,3 (C=O); 48,1 (CH_2); 20,8 (CH_3); Aromatic: 142,3; 139,2; 133,6; 131,4; 129.3; 128,0; 127,2 и 126,3

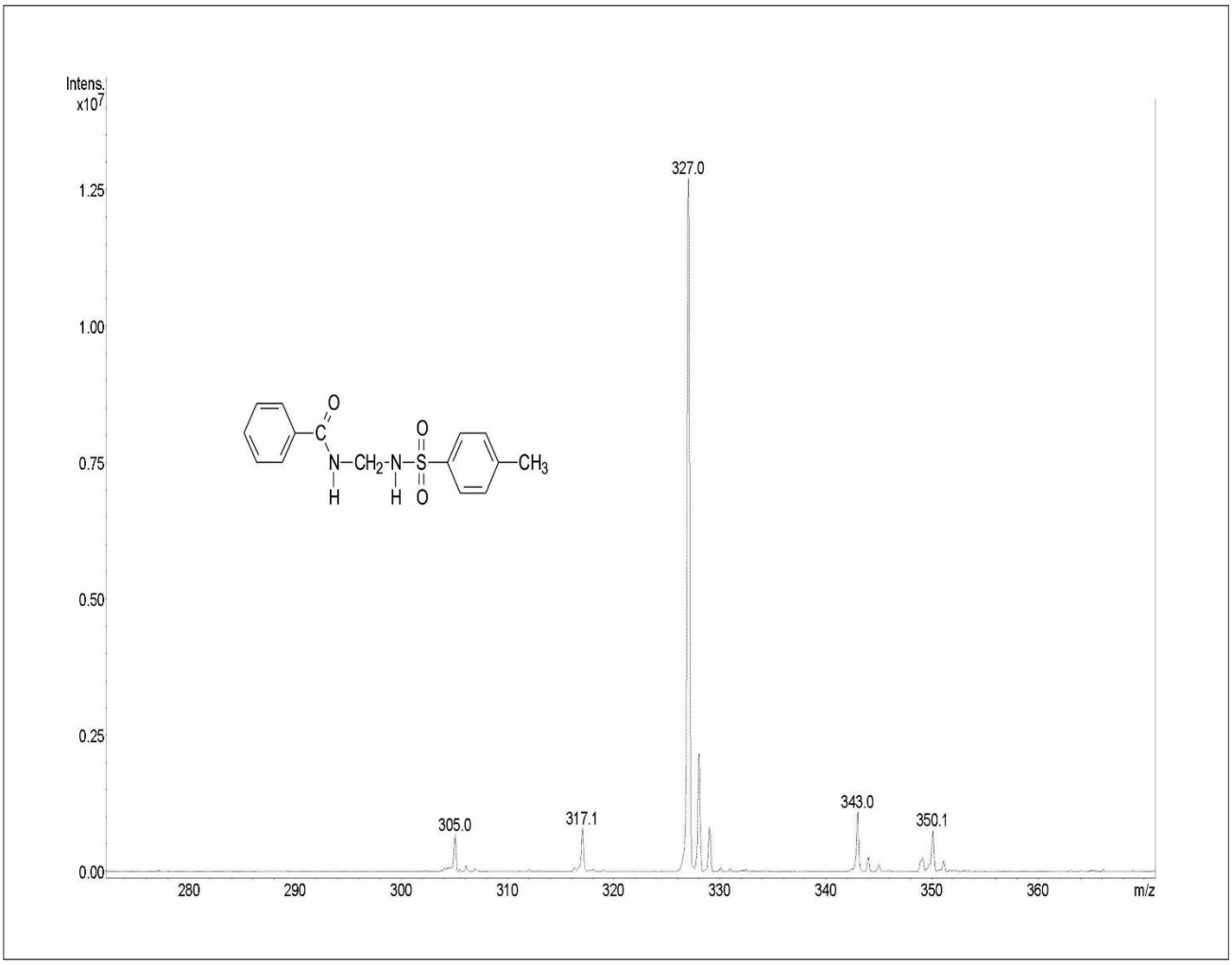


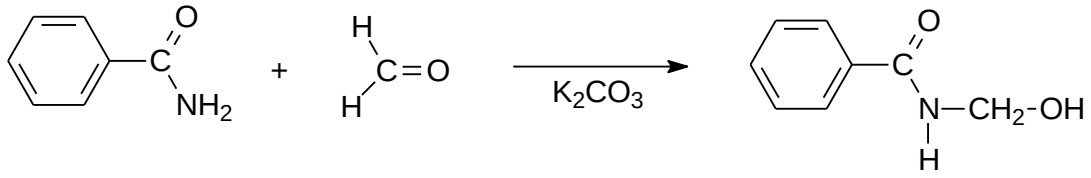
Figure 4. MS spectrum of N-benzamidomethyl-4-toluenesulfonamide

Mass spectrum (Figure 4): ESI pos. $(M + H)^+$ = 327,0 m/z

3. Results and discussion

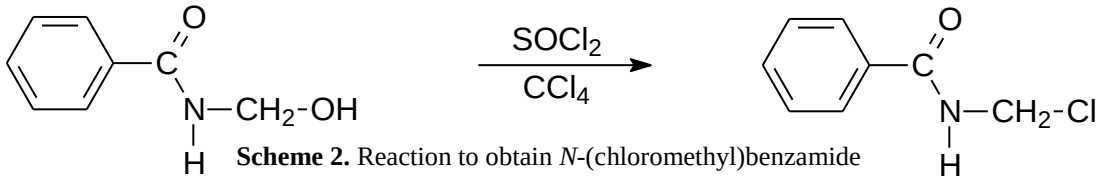
Preparation of (benzamidomethyl)triethylammonium chloride

To obtain the main reagent, *N*-(hydroxymethyl) benzamide was first synthesized, to obtain *N*-(chloromethyl) benzamide from which (benzamidomethyl)triethylammonium chloride was obtained.
The synthesis of *N*-(hydroxymethyl)benzamide was performed according to the method of Einhorn [14]. The benzamide was boiled in 35% aqueous formaldehyde in a weakly basic medium (Scheme 1) and the solution was then filtered. During the cooling of the filtrate, crystals of *N*-(hydroxymethyl)benzamide precipitated. The yield of the product was 85.3%.



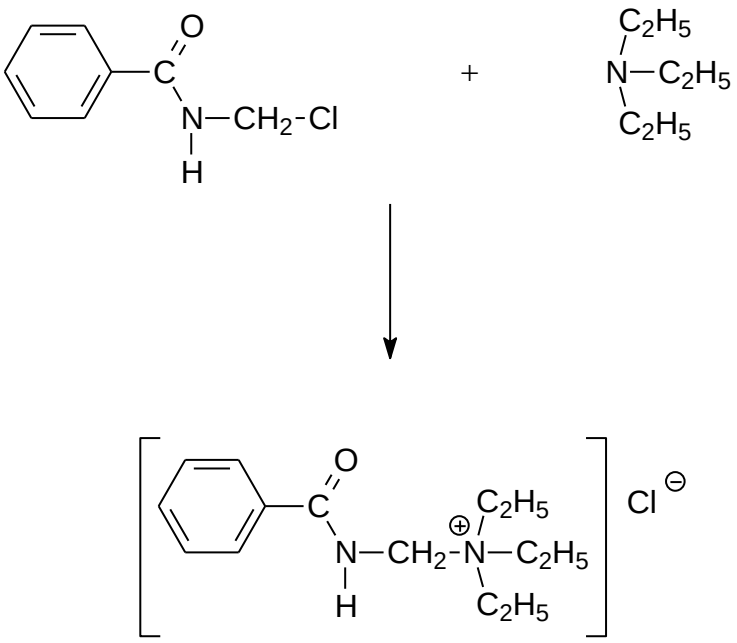
Scheme 1. Reaction to obtain N-(hydroxymethyl)benzamide

The resulting N-(hydroxymethyl)benzamide was recrystallized with water. Identification was performed by melting temperature and from the recorded IR spectrum.
In the infrared spectrum in the region 3400-3250 cm-1, an intense broadband with a transition can be observed. This band is composed of two overlapping bands due to the O-H and N-H valence vibrations. The band due to the Amide I vibration occurs at 1634 cm-1, while at 1540 cm-1 is the Amide II band originating from the vibration.
There are several methods for substituting the hydroxyl group in *N*-(hydroxymethyl)benzamide. Chlorination can be performed with PCl5 [16-18], with SOCl2 [19], or with (OCCl)2 [20], where complete anhydration of the medium in which the reaction takes place must be observed.
In this paper, the procedure of Lazarevic and coworkers [21] was applied. Specifically, to a suspension of *N*-(hydroxymethyl)benzamide in dry CCl4, the entire necessary amount of SOCl2 was added partially for 30 minutes (Scheme 2).



Scheme 2. Reaction to obtain *N*-(chloromethyl)benzamide

The obtained *N*-(chloromethyl)benzamide is a colorless crystalline substance and due to its high reactivity, it was not recrystallized and freshly prepared was used in further syntheses.
The reagent (benzamidomethyl)triethylammonium chloride that we used in our experiments was obtained in a simple way (Scheme 3).
An acetone solution of freshly prepared *N*-(chloromethyl)benzamide was suddenly added to a solution of triethylamine in acetone, and the formation of a white precipitate from the product was immediately visible.
During the synthesis, a 3 times greater amount of triethylamine was used about *N*-(chloromethyl)benzamide, and the mixture was vigorously stirred for 30 minutes.
Identification of the product was performed through the data obtained from the recorded infrared spectra.



Scheme 3. Reaction to obtain (benzamidomethyl)triethylammonium chloride

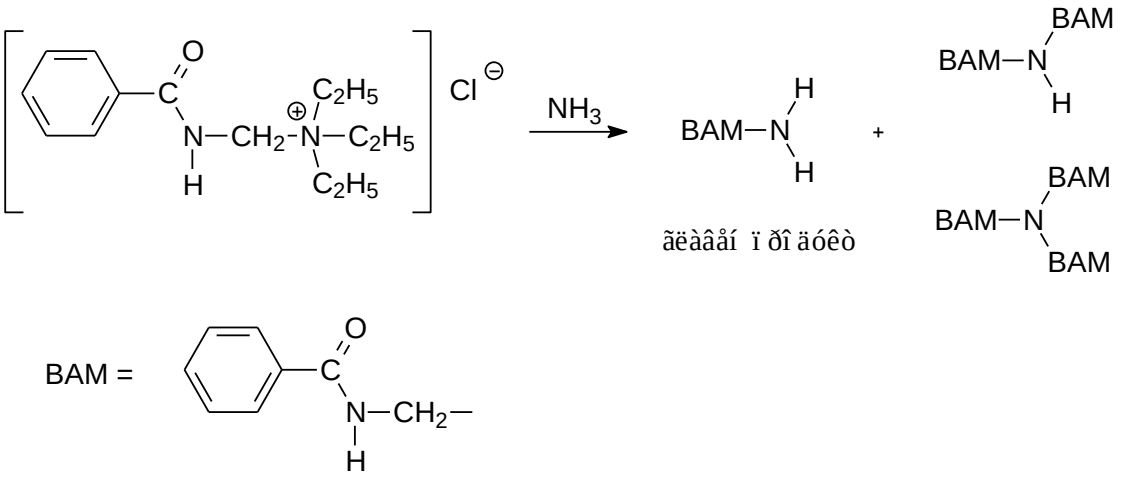
In the infrared spectrum of (benzamidomethyl)triethylammonium chloride, intense bands from 3140 to 2840 cm^{-1} can be observed. These bands are due to C-H valence vibrations from the CH_2CH_3 groups present. Amide I and Amide II vibrations give bands of strong intensity and are observed at 1662 cm^{-1} and 1546 cm^{-1}, respectively.

Preparation of N-benzamidomethyl-4-toluenesulfonamide

N-Benzamidomethyl-4-toluenesulfonamide was obtained in two different synthetic procedures. In the first procedure, reactions of 4-toluenesulfonyl chloride with (benzamidomethyl)amine were performed, and in the second procedure, reactions of 4-toluenesulfonamide with (benzamidomethyl)triethylammonium chloride were performed.

Reactions of 4-toluenesulfonyl chloride with (benzamidomethyl)amine

The (benzamidomethyl)amine required for this synthetic procedure was obtained by reacting (benzamidomethyl)triethylammonium chloride with a large amount of concentrated aqueous ammonia.
This was necessary to reduce the possibility of the formation of larger amounts of other products such as di(benzamidomethy)amine and tri(benzamidomethy)amine [56] (Scheme 4).



Scheme 4. Reaction of (benzamidomethyl)triethylammonium chloride with ammonia

An aqueous solution of (benzamidomethyl)triethylammonium chloride was added to a 37% aqueous ammonia solution with vigorous stirring. In case of cloudiness or the appearance of crystals of di(benzamidomethy)amine and tri(benzamidomethy)amine, the mixture was filtered to remove them from the solution.

A 20% aqueous solution of Na2CO3 was added to the filtrate until pH > 9. The purpose of this was to eliminate HCl that could bind to the (benzamidomethyl)amine in the form of hydrochloride. The solution was then allowed to evaporate on its own at room temperature. After evaporation, crystals, and oil droplets were obtained at the bottom of the crystallizer. Ethanol was added to this mixture to dissolve the desired product, and precipitate NaCl and unreacted Na2CO3.

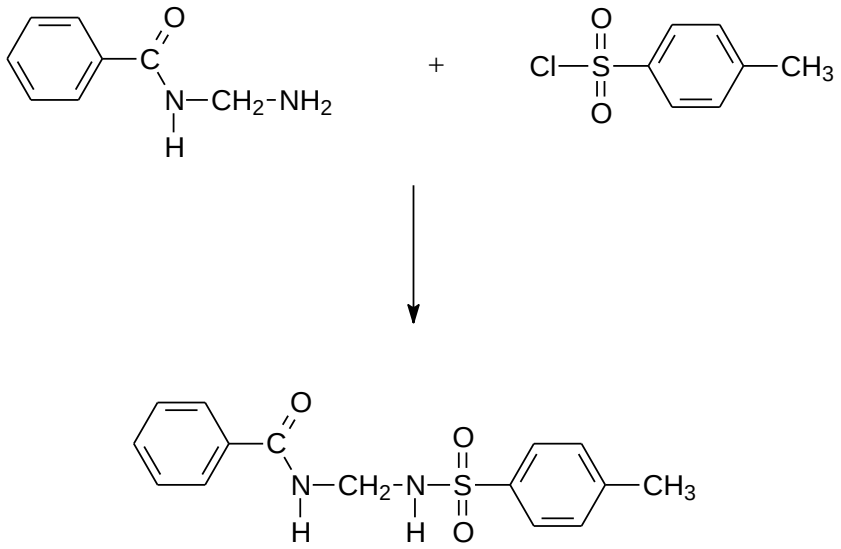
The mixture was filtered and the filtrate was allowed to evaporate at room temperature, leaving the (benzamidomethyl)amine as an oily liquid at the bottom.

The (benzamidomethyl)amine thus obtained was used for the synthesis of *N*-benzamidomethyl-4-toluenesulfonamide without prior purification.

The reaction between (benzamidomethyl)amine and 4-toluenesulfonyl chloride was carried out in aqueous medium (Scheme 5). The obtained amine was dissolved in water and during intensive mixing, well-powdered crystals of 4-toluenesulfonyl chloride were added to this solution. The molar ratio of amine to sulfonyl chloride was 2:1 to avoid the possibility of *N*, *N*-di(benzamidomethyl)-4-toluenesulfonamide formation. Colorless crystals of the product that formed over time were separated by filtration under reduced pressure.

Recrystallization was performed with ethanol. The yield of the pure product was 83% with a melting point of 163–164 °C. The structure of the obtained product was confirmed through the data obtained from the mass, FTIR, 1H-NMR, and 13C-NMR spectra.

In the IR spectrum of the obtained derivative two bands were observed at 3337 cm-1 and 3290 cm-1 from the valence vibrations of the two N-H bonds. A band at 1640 cm-1 was indicative of the presence of Amide I vibration, and a band at 1530 cm-1 was indicative of the presence of Amide II vibration in the product structure. A band at 1162 cm-1 from the S=O bond was also observed in the spectrum.



Scheme 5. Reaction of (benzamidomethyl)amine and toluenesulfonyl chloride

That it is the expected product was confirmed by the 1H-NMR spectrum of this compound as well as by the ratio of the integrals of the signals in it (Figure 6).

A triplet at 8.81 ppm and 8.28 ppm from the protons of the two NH groups, 9 signals in the region from 7.71 ppm to 7.24 ppm from the aromatic protons, a triplet from the CH2 group at 4.46 ppm, and a singlet from CH3 group at 2.27 ppm.

In the 13C–NMR spectrum, 8 bands of the aromatic C atoms from 126.3 ppm to 142.3 ppm, one band of the C atom of the carbonyl group of C=O at 166.3 ppm as well as 48.1 ppm and 20.8 ppm from the carbon atoms of the CH2 and CH3 groups, respectively.

In the ESI MS Spectrum, the molecular ion [M+H] + was registered at 305.0 m/z, considering the molecular mass of *N*-benzamidomethyl-4-toluenesulfonamide which is 304.4 g/mol, which was another confirmation of the structure of the product.

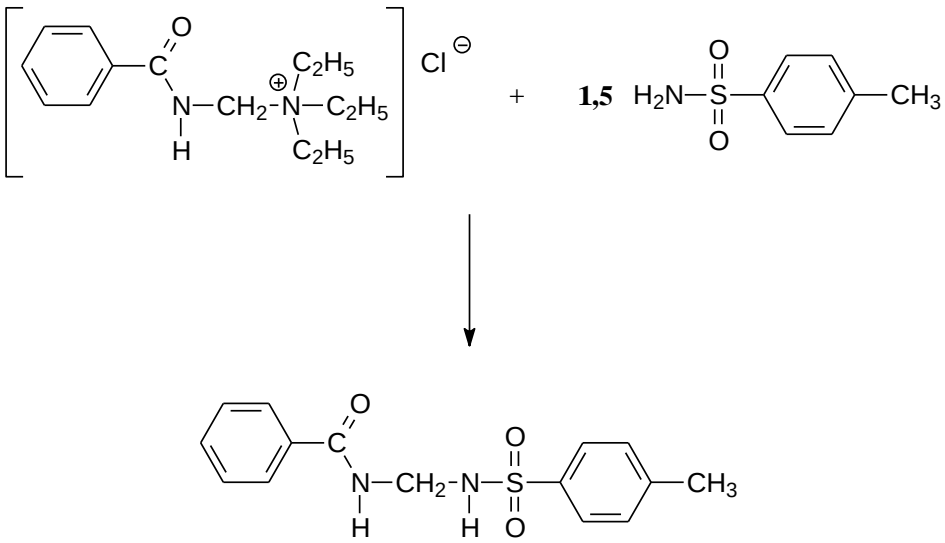
Reactions of 4-toluenesulfonamide with (benzamidomethyl)triethylammonium chloride

The reaction of toluenesulfonamide and (benzamidomethyl)triethylammonium chloride in a molar ratio of 1.5: 1 was carried out in the water as the medium (Scheme 6).

To an ethanolic solution of toluene, sulfonamide was added an aqueous solution of (benzamidomethyl)triethylammonium chloride. After stirring at room temperature for 4 hours, colorless crystals of the product were observed.

The pH of the solution was monitored simultaneously. If the solution became more acidic, a few drops of triethylamine (TEA) were added until pH ≥ 9. After the fourth hour, water was added to precipitate all the product, but the excess sulfonamide was also partially precipitated.

The yield of the air-dried crude product was 91.3% with a melting point of 162.5–164 °C.



Scheme 6. Reaction of toluenesulfonamide and (benzamidomethyl)triethylammonium chloride

Since toluenesulfonamide is well soluble in ethanol, unlike the product, recrystallization was performed with ethanol. Pure *N*-(benzamidomethyl)-4-toluenesulfonamide was in the form of colorless small crystals with a melting point of 163–164 °C. The yield after recrystallization was 90.1%.

UV spectroscopic characteristics of the obtained compound

—— *N*- benzamidomethyl-4-toluenesulfonamide
—— 4- Toluenesulfonamide

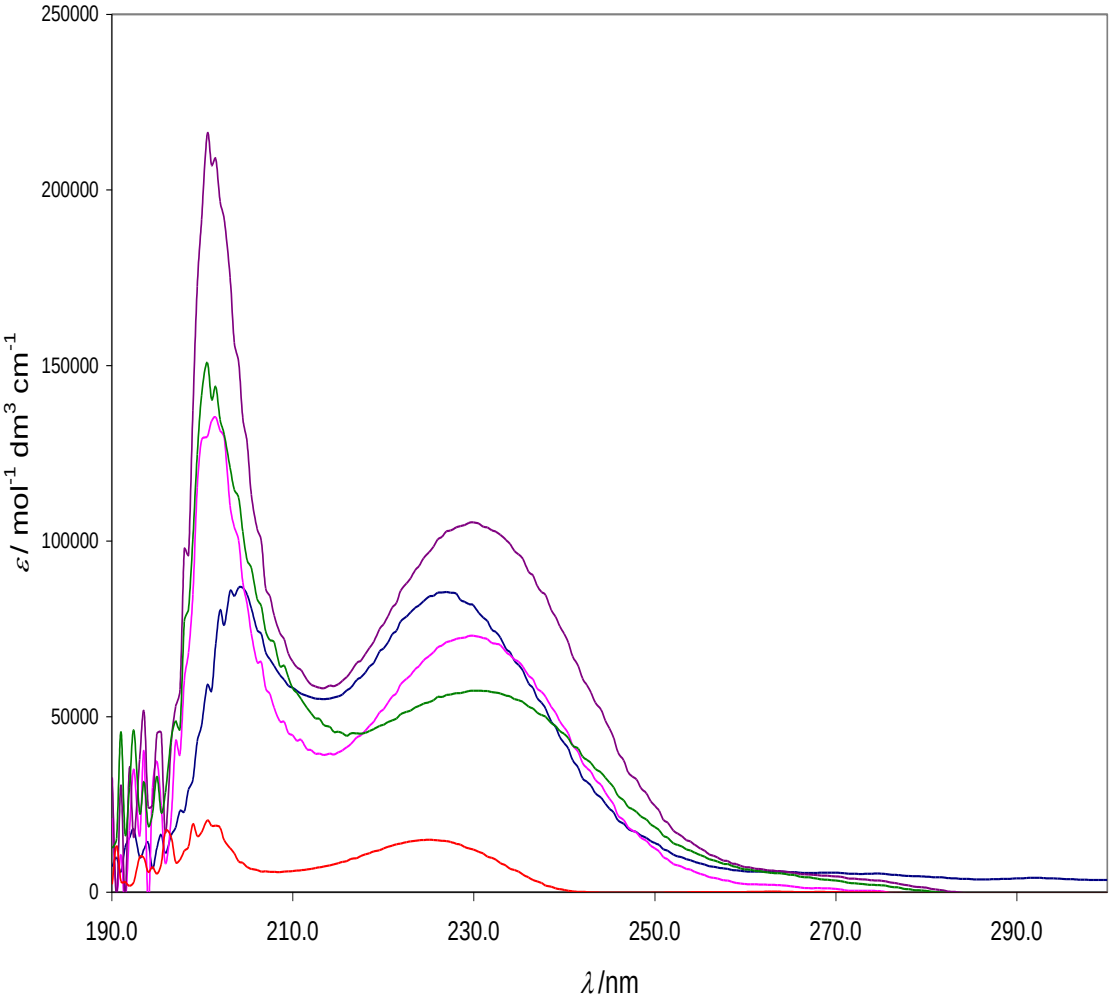


Figure 5. Dependence of the molar absorption coefficient on the wavelength of TSA and the synthesized compound

The UV spectra of *N*-benzamidomethyl-4-toluenesulfonamide were also recorded in the scientific paper. For an appropriate comparison of the spectroscopic characteristics of the synthesized compounds, in their UV spectra instead of the absorbance, values for the molar absorption coefficient ε/mol^{-1} dm^3 cm^{-1} are given on the ordinate (Figure 5).

The following table gives the corresponding characteristics for absorption bands, i.e., absorption maxima and the logarithmic values of the molar absorption coefficients.

Table 1. Position of the absorption bands in the UV spectra of the synthesized compounds

compound	□max /nm			
	□max /nm	log {ε}*	□max /nm	log {ε}*
benzamid[22]	194	4,42	227	3,91
4- Toluenesulfonamide	200,5	4,31	225	4,18
N- benzamidomethyl-4-toluenesulfonamide	203,0	4,93	227	4,93

** Values of log [ε/(mol-1 dm3 cm-1)] are determined in ethanol.*

If we make a comparison about the spectrum of 4-toluenesulfonamide, it is noticeable that the absorption maxima of the two bands in the obtained benzamidomethyl derivatives are shifted bathochromically, accompanied by a strongly pronounced increase in absorption. At the same time, the position of the absorption maxima (Table 1) is close to that of benzamide, considering the fact that mono and disubstituted benzene derivatives absorb at higher wavelengths than benzene.

4. Conclusion

The problem dealt with in this paper is from the field of organic synthetic chemistry. This research work aimed to investigate the possible and most efficient synthetic routes for obtaining benzamidomethyl derivatives of toluenesulfonamide as an introduction to further research for obtaining new *N*-benzamidomethyl sulfonamide derivatives with potential biological activity.

One of the synthetic procedures included benzamidomethylation reactions of 4-toluenesulfonamide with (benzamidomethyl)triethylammonium chloride, as well as some N-substituted derivatives of 4-toluenesulfonamide.

For this purpose, at the beginning, (benzamidomethyl)triethylammonium chloride was synthesized, which has been used as a reagent for many years in the laboratory of the Institute of Organic Chemistry of the Institute of Chemistry at the Faculty of Science and Mathematics in Skopje.

The other synthetic procedure included reactions of 4-toluenesulfonyl chlorides with (benzamidomethyl)amine, i.e. some of its *N*-substituted derivatives. Toluenesulfonyl chloride was purchased commercially, while benzamidomethyl amines were synthesized according to already-known procedures.

The following can be concluded from the results obtained during the preparation of this scientific paper:

- In the reaction of 4-toluenesulfonamide with (benzamidomethyl)triethylammonium chloride, as well as in the reaction of 4-toluenesulfonyl chloride with (benzamidomethyl)amine, the following was obtained: ***N*–benzamidomethyl-4-toluenesulfonamide**
- The structure of the obtained compound was confirmed and characterized by the data obtained from their FTIR, 1H–NMR, 13C–NMR, UV and MS spectrometry,
- In the framework of the scientific work, N-benzamidomethyl-4-toluenesulfonamide was synthesized according to various synthetic procedures, for which there were no previously known literature data,
- The results and conclusions obtained in this research work will be a roadmap for future research to obtain new benzamidomethyl derivatives of sulfonamides with potential biological activity,
- The paper is also very useful to the public in the direction of obtaining new compounds with potential biological activity that would be useful for the pharmaceutical industry.

References

[1]. Delgado, J.N.; Remers, W.H., *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th Ed., William & Wilkins, USA, 1998, p.223.
[2]. Domakg , E., Disch. Med. Wochenschr, 1935, 61, 250.
[3]. V.K Pandei, R.P.Misra, Indian drugs, 1986, 23(8), 426-5; CA 10696319d.
[4]. V.K Pandei, P.Garu, B.L. Chowdhuru, Biol.Mem., 1987, 13(1)83-7, CA 110 57562d.
[5]. K. Kondo, I. Inoue, J.Org.Chem., 1980, 45, 1577-81.
[6]. V.K Pandei, N.Raj, Pharmacol.Res.Commun, 1986, 18(10)923-33, CA 106 96319s.
[7]. J.A. Alter, Span. 444, 345(cl.CO7F), 01 Oct 1977; CA 8975372u.
[8]. A. Bhatia, S.C. Chaturverdi, J.G. Asthana, Indian J. Pharm. Sci., 1981, 43(2), 49-51; CA 95 150119w.
[9]. J.P Clayton, D. Kenneth, A.W.C. Guest, Ger. Offen. 2,326,795(Cl.C07d), 06 Dec 1973 CA 8059950q.
[10]. G. Franceshi , M. Foglio, F.Arcamone, Ger. Offen . 2,406,817(Cl.C07d), 22 Aug 1974 CA 81152218n.

[11]. E. Lukevis, S.Germane, M. Trusule, V.F. Mironov, T.K. Gar, O.A.Dambrova N.A. Viktorov, Khim-Farm. Zh, 1988, 22(2), 163-7, CA 109214s.
[12]. G. B. Barlin, L.P.Davies, S.J. Ireland, M.M.L. Ngu,J.Zhang, Aus. J. Chem., 1992, 45(4), 731-49; CA 116255565u.
[13]. L.F Kashukin, V.S. Brovarets, O.B. Smolii, V.V. Kurg, L/V. Budnik, B.S. Drach, Zh.Obshch. Khim., 1991,61(12), 2679-84;Ca11748707x.
[14]. A. Einhorn, E. Bischkopff, B. Szelinski, Ann., 1905, 343, 223-52;
[15]. Popovski, E.; Klisarova, L.; Vikic-Topic, D. Benzamidomethylation with (Benzamidomethyl)-triethylammonium Chloride 2. A Simple Method for Benzamidomethylation of Thiols, Amines and Carboxylic acids. Molecules 2000, 5, 927-936.
[16]. H. Bohme, R. Broese, A. Dick, F. Eiden, D. Schunemann, Ber. 1959, 92, 1599-1607;
[17]. H. Hellmann, Angew. Chem., 1957, 463-471;
[18]. P.A. Ivanov, E.I. Popov, V.F. Celivanov, B.V. Gidaspov, Eur. Org. Him., 1972, 8(11), 2371-3;
[19]. B.S. Draz, Ï.P. Sviridov, A.V. Kirsanov, Eur. Org. Him., 1972, 8(9), 1825-7;
[20]. H. Bohme, K.H. Ahrens, E. Tippmann, Arch. Pharm. (Weinheim), 1977, 310, 242-8;
[21]. M.J. Pulwer, T.M. Balthazor, Synthetic Communications, 1986, 16(7), 733-9;
[22]. Goran M. Stojkovic, Examination of the protonation reactions of some amides in a strongly acidic environment using ultraviolet spectroscopy, Doctoral Dissertation, Faculty of Science and Mathematics, University "St. Cyril and Methodius", Skopje, 2006.